substitute or therapeutic hemoglobin that is physiologically acceptable for use in clinical or veterinary medicine according to methods know in the art. See, for example, R.M. Winslow, et al. Eds. Blood Substitutes Physiological Basis of Efficacy, pp. 82-84 (Birkhauser, Boston, Mass.) (1995), the disclosure of which is incorporated herein by reference. The hemoglobin of the present invention may also be advantageously used as a treatment for conditions such as septic shock, prevention of anaphylactic shock during dialysis.

In the Claims:

Please cancel claims 1-19, 30, and 33-35, without prejudice.

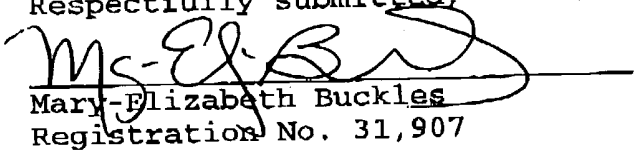
REMARKS

Applicants note that an initial computer readable form (CRF) copy of the Sequence Listing for the above-referenced application, a paper copy thereof, and a copy of the Sequence Listing from parent application Serial Number 09/598,218 were filed March 28, 2002.

Kindly enter the above amendments prior to calculation of the filing fee. It is believed that the present application is in condition for allowance and notice to such effect is respectfully requested. If the Examiner believes that additional issues need to be resolved before this application can be passed to issue, the undersigned invites the Examiner to contact her at

the telephone number provided below.

Respectfully submitted,



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Filed: July 3, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The initial paragraph in the application beginning "This application" after the title on page 1 of the application is being inserted as follows:

-- This application hereby claims the benefit under 35 U.S.C. §120 of earlier filed U.S. Patent Application Serial No. 09/598,218 filed June 21, 2000. --

The paragraph beginning "Hemoglobin is" at page 2, line 3 has been amended as follows:

Hemoglobin is the oxygen-carrying component of blood, circulated through the blood stream inside erythrocytes (red blood cells). Human normal adult hemoglobin ("Hb A") is a tetrameric protein with a molecular weight of about 64,500 containing two identical α chains having 141 amino acid residues each and two identical β chains having 146 amino acid residues each, with each also bearing prosthetic groups known as hemes. The erythrocytes help maintain hemoglobin in its reduced, functional form. The heme-iron atom is susceptible to oxidation, but may be reduced again by one of two systems within the erythrocyte, the cytochrome b_5, and glutathione reduction systems. For a review on hemoglobin, see, Dickerson, R.E., et

al. Hemoglobin: Structure, Function, Evolution, and Pathology, p. 22-24, Benjamin/Cummings, Menlo Park, CA (1983) (hereinafter "Dickerson, et al. (1983)"), the disclosure of which is incorporated herein by reference.

The paragraph beginning "The cooperative" at page 5, line 4 has been amended as follows:

The cooperative oxygenation of Hb, as measured by the Hill coefficient ("n_{max}") is a convenient measure of its oxygenation properties. See, Dickerson, et al. (1983). Hb A has an n_{max} value of approximately 3 in its binding with O_2 under usual experimental conditions. Human abnormal Hbs with amino acid substitutions in the $\alpha_1\beta_2$ (or $\alpha_2\beta_1$) subunit interface generally result in high oxygen affinity and reduced cooperativity in O_2 binding compared to Hb A. See, for example, Dickerson, et al. (1983); Bunn, et al (1986) and Perutz, M.F., et al. Mechanisms of Cooperativity and Allosteric Regulation in Proteins pp. 19-29, Cambridge University Press (1990), the disclosure of which is incorporated herein by reference.

The paragraph beginning "The exchangeable" at page 36, line 1 has been amended as follows:

The exchangeable proton resonances of the Hb molecule arise from the exchangeable protons in the subunit interfaces. Of special interest to the present invention are the exchangeable

proton resonances at 14.2, 12.9, 12.1, 11.2, and 10.7 ppm from DSS, which have been characterized as the inter-subunit H-bonds in the $\alpha_1\beta_1$ and $\alpha_1\beta_2$ subunit interfaces in both deoxy (T) and/or oxy (R) states of Hb A (Russu, et al (1987); Fung, et al. (1975)); and Ho (1992), the disclosures of which are incorporated herein by reference). The resonances at 12.9 ppm and 12.1 ppm from DSS have been assigned to the H-bonds between α122His and β35Tyr, and α103His and β131GIn, respectively (see Russu, et al. (1987) and Simplaceanu, et al. Biophys. J. [(in press)] 79:1146 (2000) (hereinafter "Simplaceanu, et al. (2000)"). In the spectra of rHbCO (βN108Q) and rHbCO (αL29F, βN108Q) (as seen in Figure 6A), three resonances instead of one occur corresponding to the chemical shift of HbCO A at 12.1 ppm. The main peak occurs at 12.0 ppm, with a shoulder at 11. 8 ppm and an extra resonance at 12.3 ppm. The intensities of the resonances at 12.3 and 11.8 ppm are not even 1/10 of the ones at 12.0 ppm and at 12.9 ppm, indicating that these two extra resonances are unlikely to be contributed by additional protons. The sum of the integrated areas of the resonances at 11.8, 12.0, and 12.3 ppm is about the same as the area of the single resonance at 12.9 ppm, suggesting the coexistence of three conformers of rHb (βN108Q) in CO form.

The paragraph beginning "Appropriately cross-linked" at page 47, line 16 has been amended as follows:

Appropriately cross-linked rHb (βN108Q) and/or rHb (βL105W) can be incorporated into a hemoglobin-based blood substitute or therapeutic hemoglobin that is physiologically acceptable for use in clinical or veterinary medicine according to methods know in the art. See, for example, R.M. Winslow, et al. Eds. Blood Substitutes Physiological Basis of Efficacy, pp. 82-84 (Birkhauser, Boston, Mass.) (1995), the disclosure of which is incorporated herein by reference. The hemoglobin of the present invention may also be advantageously used as a treatment for conditions such as septic shock, prevention of anaphylactic shock during dialysis.

In the Claims:

Please cancel claims 1-19, 30, and 33-35, without prejudice.